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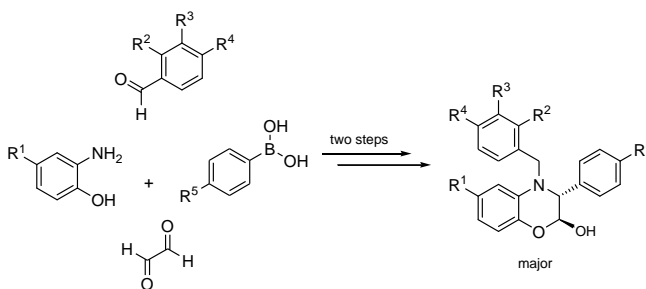
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## Graphical Abstract

### A new and efficient one-pot synthesis of 2-hydroxy-1,4-dihydrobenzoxazines via a three-component Petasis reaction

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# A new and efficient one-pot synthesis of 2-hydroxy-1,4-dihydrobenzoxazines via a three-component Petasis reaction

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**Abstract**— The secondary amines synthesized by the reaction between 2-aminophenols and aromatic aldehydes, via the reduction of the corresponding imines, were employed in the synthesis of new 2-hydroxy-2*H*-1,4-benzoxazine derivatives via a one-pot Petasis multicomponent reaction in good to excellent yields.

Multicomponent reactions are highly efficient and atom-economic transformations in synthetic organic chemistry.<sup>1</sup> They can be used for constructing an array of compound libraries in the medicinal chemistry field.

The Petasis reaction (the application of a boronic acid nucleophile in the Mannich reaction) has received increasing attention due to its utility as a powerful and convenient method for the synthesis of functionalized amine derivatives,<sup>2</sup> such as  $\alpha$ -amino carboxylic acids and derivatives,<sup>3</sup>  $\beta$ -amino alcohols,<sup>4</sup> allyl amines,<sup>5</sup> and various heterocyclic compounds,<sup>6</sup> while new applications continue to be developed.<sup>7</sup>

This one-step, three-component reaction involves coupling of an amine, an organoboronic acid, and a carbonyl compound functionalized at the  $\alpha$ -position to give the corresponding amine derivative in a short and experimentally simple process. Along with the accessibility of reagents and mild reaction conditions, this approach is an attractive alternative to other methodologies.

A large variety of alkenyl, aryl, and heteroaryl boronic acids, various primary and secondary amine derivatives (e.g., diamines, *N*-hydroxylamines, *N*-sulfinyl amines, hydrazines) and functionalized carbonyl compounds (e.g.,  $\alpha$ -keto acids and  $\alpha$ -hydroxy aldehydes) have been shown to participate in this reaction with success.<sup>2</sup> The reaction can be carried out in many different solvents, usually CH<sub>2</sub>Cl<sub>2</sub>, toluene, alcohols as methanol or hexafluoroisopropanol and also in water.<sup>8</sup>

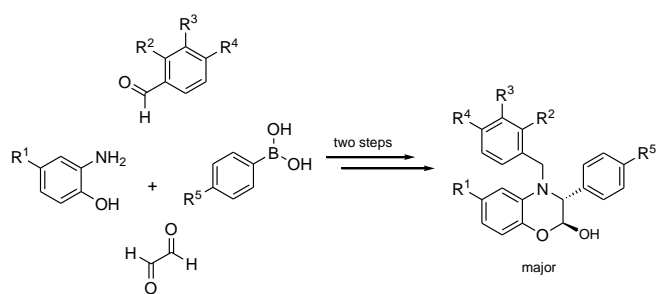
Additionally, the 1,4-benzoxazine<sup>7</sup> moiety is an integral part of several naturally occurring substances. For example, various glycosides of the 2-hydroxy-2*H*-1,4-benzoxazines skeletons have been found to occur in *graminaceous* plants such as maize, wheat, rye, and rice, and have been suggested to act as plant resistance factors against microbial diseases and insects.<sup>8</sup> The 1,4-benzoxazine moiety was also found in various antibiotics such as C-1027.<sup>9</sup>

Generally, 1,4-benzoxazine compounds were usually synthesized via a multistep process, such as the cyclocondensation of *o*-aminophenols with suitable dihalo derivatives,<sup>10</sup> cyclocondensation of *o*-aminophenols with  $\alpha$ -halo-acyl bromides followed by carbonyl group reduction with BH<sub>3</sub>,<sup>11</sup> and alkylation of *o*-nitrophenol with a  $\alpha$ -haloaldehyde followed by reductive cyclization.<sup>12</sup> Alternatively, these 1,4-benzoxazine moieties can be prepared via ring-opening of an epoxide with *o*-halosulfonamides followed by cyclization<sup>13</sup> or by ring-opening of an epoxide with *o*-aminophenols followed by cyclocondensation.<sup>14</sup>

As part of our ongoing research on multicomponent reactions,<sup>15</sup> we have developed, a new alternative route to the conventional multistep synthesis of 2-hydroxy-1,4-benzoxazines via a Petasis multicomponent reaction (Scheme 1).

**Keywords:** 2-Hydroxy-2*H*-1,4-benzoxazine, Petasis reaction, Secondary amines, Multicomponent reaction.

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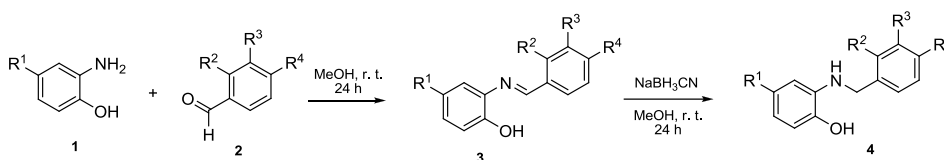
Scheme 1.

The proposed strategy involves the use of 2-(benzylamino)phenols **4** as reactant. They were initially prepared in high yields by condensation of substituted 2-aminophenols **1** and benzaldehydes **2** followed by reduction in a one-pot process. These key intermediates

subsequently reacted with aryl boronic acids **5** and glyoxal **6** in methanol at ambient temperature to afford the target compounds **7** in good yields.

We began our research by preparing secondary amines **4**. Indeed, 2-(4-methoxybenzylamino)phenol (**4a**) was obtained from the condensation of 2-aminophenol (**1a**) (1 equiv.) with benzaldehyde (**2a**) (1 equiv.) in dry methanol or dichloromethane at room temperature. The reaction proceeded smoothly and provided, after 24 hours, an excellent yield of the corresponding imine (**3a**). The addition of an excess of NaBH<sub>3</sub>CN and stirring the mixture for 24 hours at ambient temperature resulted in the formation of the desired secondary amine **4a** in very high yield. This process was generalized to synthesize various substituted amines as shown in Table 1. Most of the reactions were found to proceed cleanly in about 60-90% yield of the products. The time taken for the completion of the reactions varying between 18 and 24 hours (Scheme 2).

Scheme 2.

Table 1. Synthesis of 2-(arylmethylamino)phenols **4**.<sup>a</sup>

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	2-(Arylmethylamino)phenol	Yield <sup>b</sup> (%)	M.p. (°C)
1	H	H	H	OCH <sub>3</sub>		83	104-106
2	CH <sub>3</sub>	H	H	OCH <sub>3</sub>		84	136-138
3	Cl	H	H	OCH <sub>3</sub>		60	148-150
4	CH <sub>3</sub>	H	H	Br		90	86-90
5	H	NO <sub>2</sub>	H	H		75	90-92
6	CH <sub>3</sub>	H	NO <sub>2</sub>	H		95	120-122

<sup>a</sup> Reactions conditions: **1** (1 mmol), **2** (1 mmol), MeOH (5 ml), r.t., 24 h, then NaBH<sub>3</sub>CN (3 mmol) was added and stirring was continued for 24 h. <sup>b</sup> Isolated yields.

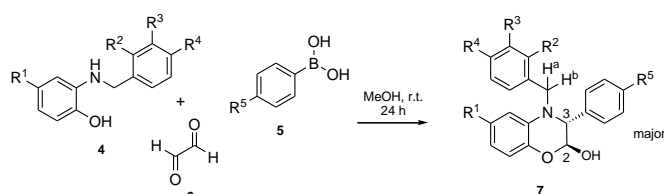
Our investigations on the Petasis process identified dichloromethane at room temperature as the optimum medium for the reaction of 2-(4-methoxybenzylamino)-4-methylphenol **4b** with phenylboronic acid **5a** and glyoxal **6**. These conditions provided useful yields and reasonable reaction times. Further, we observed improved results by employing methanol as the solvent, resulting in a yield of 89% of the desired 1,4-benzoxazine **7b** (Table 2, entry 2). Despite the relatively long reaction times proving to be a limitation of room temperature processes, high yields of the desired product were achieved (Scheme 3).

On the basis of these results, we have explored the substrate scope and limitations. A series of diverse 1,4-benzoxazines bearing different substitution patterns **7a-i** were prepared in moderate to excellent yields by reactions of aryl boronic acids **5** with 2-(arylmethylamino)phenols **4a-f** and glyoxal **6**, and all the results are listed in Table 2.<sup>16</sup> It was observed that the reactions of phenylboronic acid

furnished the products in higher yields than those with 4-methylphenylboronic acid.

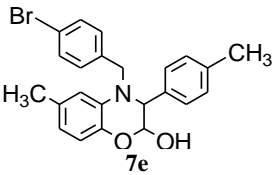
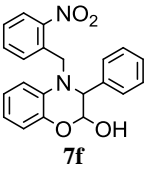
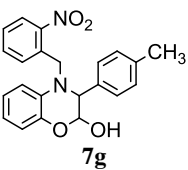
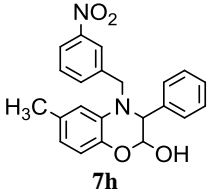
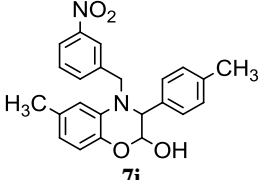
The scope of the reaction with regard to the secondary amines was also explored. Electron-donating substituents underwent the reaction with best yields (Table 2, entries 1-3). The presence of an electron-withdrawing group caused a reduction in yield (entries 4 and 5), even more significant in the case of a nitro substituent (entries 6-9). As outlined in Table 2, all these compounds were obtained as mixtures of diastereoisomers with the ratio depending on substituents in different positions of the 1,4-benzoxazine core. The assignment of a relative trans configuration for the major isomer was secured by X-ray crystallographic analysis of **7f**, the hydroxyl group being in an axial position in the solid state (Figure 1).<sup>17</sup>

**Scheme 3.**



**Table 2.** The Petasis reaction of secondary amines **4**, aryl boronic acids **5**, and glyoxal (**6**).<sup>a</sup>

Entry	Secondary amine	R <sup>5</sup>	1,4-Benzoxazine	M.p. (° C)	Yield <sup>b</sup> (%)	dr <sup>c</sup>
1	<b>4a</b>	CH <sub>3</sub>	 <b>7a</b>	oil	76	95:5
2	<b>4b</b>	H	 <b>7b</b>	oil	89	86:14
3	<b>4c</b>	H	 <b>7c</b>	oil	70	88:12
4	<b>4d</b>	H	 <b>7d</b>	131-132	72	90:10

5	4d	CH <sub>3</sub>	 7e	132-134	86	97:3
6	4e	H	 7f	170-171	56	83:17
7	4e	CH <sub>3</sub>	 7g	141-143	46	90:10
8	4f	H	 7h	125-127	64	85:15
9	4f	CH <sub>3</sub>	 7i	160-162	38	95:5

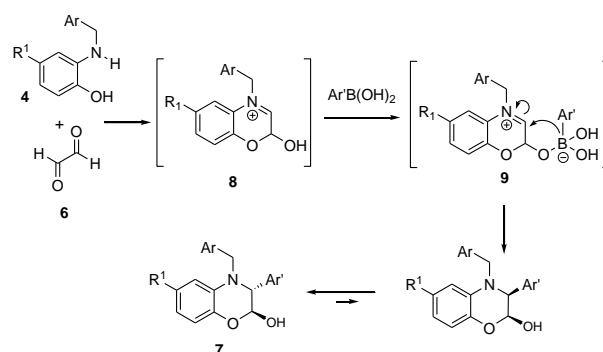
<sup>a</sup> Reactions conditions: **4** (1 mmol), **5** (1 mmol), **6** (1 mmol), MeOH (5 ml), r.t., 24 h. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by <sup>1</sup>H NMR spectroscopy.

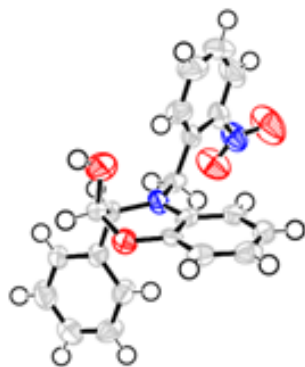
Considering previous studies on the borono-Mannich reaction with glyoxal,<sup>6d, 18</sup> a plausible pathway for the formation of compound **7** is proposed in Scheme 4. This involves an initial condensation of 2-(arylmethylamino) phenols **4** with glyoxal **6** to give a cyclic iminium intermediate **8**. The coordination between the hydroxyl function of this species with the boron atom of **5** leads to the formation of a tetracoordinate boron intermediate **9** that undergoes an irreversible transfer of the aryl group to generate the *cis* 2-hydroxy-1,4-benzoxazines **7**. Equilibration of the hemiacetal after this intramolecular delivery affords the *trans* isomer.

In summary, we have developed a new and general approach for the library synthesis of 1,4-benzoxazine derivatives via Petasis reactions of easily available 2-(arylmethylamino)phenols with glyoxal and various boronic acids without any catalyst. Our method allows access to a wide range of 2-hydroxy-1,4-benzoxazines, which may be useful compounds for medicinal and materials chemistry. Simple substrates,

good yields, and operational simplicity are significant advantages of this procedure. Further investigations regarding the exact mechanism of this Petasis condensation and the further transformation of these heterocycles are currently in progress.

**Scheme 4.**





**Figure 1.** X-ray crystal structure (ORTEP) of compound 7f (CCDC 1012140). Crystal data: C<sub>21</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>, Mr = 362.37; orthorhombic, Pna2<sub>1</sub>; Hall symbol: P 2c-2n; a = 12.7332 (14) Å; b = 14.2777 (14) Å; c = 19.003 (2) Å; V = 3454.8 (6) Å<sup>3</sup>, Z = 8.

## Acknowledgment

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2014.07.093>.

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- Typical experimental procedure for the synthesis of 2-(arylamino)phenols **4**: A mixture of 2-aminophenol derivative (**1**) (3 mmol) and aromatic aldehyde (**2**) (3 mmol) in MeOH (10 ml) was stirred at room temperature for 24 h (monitored by TLC). After formation of the imine **3**, NaBH<sub>3</sub>CN (9 mmol) and HCl (a few drops), were added and stirring was continued for 24 h. After the reaction was complete, the mixture was poured into ice water. The resulting precipitate was filtered, washed with H<sub>2</sub>O, and dried. The resulting amine was obtained in very high purity and in excellent yield.
- 2-(4-Methoxybenzylamino)phenol (**4a**): IR (KBr) ν: 3333; 1601 cm<sup>-1</sup>. <sup>1</sup>H NMR (250 MHz, DMSO-*d*<sub>6</sub>) δ: 9.34 (s, 1H, NH); 7.27 (d, 2H, *J*=7.9 Hz, CH arom.); 6.87 (d, 2H, *J*=7.9 Hz, CH arom.); 6.67 (d, 1H, *J*=7.1 Hz, CH arom.); 6.56 (t, 1H, *J*=7.1 Hz, CH arom.); 6.40 (d, 2H, *J*=7.1 Hz, CH arom.); 5.17 (s, 1H, OH); 4.20 (s, 2H, CH<sub>2</sub>); 3.71 (s, 3H, OCH<sub>3</sub>). <sup>13</sup>C NMR (63 MHz, DMSO-*d*<sub>6</sub>) δ: 158.4; 144.5; 137.6; 132.7; 128.8; 120.0; 116.2; 114.1; 113.7; 110.6; 55.4; 46.4.
- Typical experimental procedure for the synthesis of 1,4-benzoxazine derivatives **7**: A mixture of 2-(arylmethylamino)phenol **4** (1 mmol), boronic acid **5** (1 mmol) and glyoxal **6** (1 mmol) in MeOH (5 mL) was stirred at room temperature for 24 h. The solvent was removed in vacuo to give crude product **7**, which was purified by flash chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>). Spectroscopic data for the major isomer of

4-(2-Nitrobenzyl)-3-phenyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-ol (**7f**): IR (KBr):  $\nu$ : 3429, 2920, 1608, 1512, 1250, 1036  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.09 (d, 1H,  $J=7.5$  Hz, CH arom); 7.91 (d, 1H,  $J=7.5$  Hz, CH arom.); 7.56 (t, 1H,  $J=7.5$  Hz, CH arom.); 7.42 (t, 1H,  $J=7.5$  Hz, CH arom.); 7.33-7.30 (m, 3H, CH arom.); 7.21-7.18 (m, 2H, CH arom.); 6.92-6.83 (m, 2H, H arom.); 6.74-6.67 (m, 1H, CH arom.); 6.45 (d, 1H,  $J=7.5$  Hz, CH arom.); 5.60 (br s, 1H,  $\text{H}_2$ ); 5.06 (d, 1H,  $J=18.5$  Hz,  $\text{H}_b$ ); 4.62 (d, 1H,  $J=18.5$  Hz,  $\text{H}_a$ ); 4.51 (br s, 1H,  $\text{H}_3$ ); 3.26 (s, 1H, OH).  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ )  $\delta$ : 148.1; 141.1; 139.7; 138.3; 134.1; 134.0; 133.7; 129.0; 130.0; 128.3; 128.0; 126.9; 125.3; 122.9; 117.9; 117.5; 110.6; 92.7; 64.3; 50.2. HRMS:  $(\text{M}+\text{H})^+$ , found 363.1352,  $\text{C}_{21}\text{H}_{19}\text{N}_2\text{O}_4$  requires 363.1346.

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